CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217836Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 16, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217836
Product Name, Dosage Form, and Strength:	Qlosi (pilocarpine hydrochloride) ophthalmic solution , 0.4%
Applicant/Sponsor Name:	Orasis Pharmaceuticals, Ltd.
TTT ID #:	2023-3264-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised pouch and carton labeling received on October 13, 2023 for Qlosi. The Division of Ophthalmology (DO) requested that we review the revised pouch and carton labeling for Qlosi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

The Applicant implemented most of our recommendations; however, we note that the Applicant did not accept our recommendation to revise the design of the lowercase letter 'l' presented with a dot beneath it. The design is similar to that used for the lowercase letter 'i' in the design for the proprietary name 'Qlosi,' which may lead to misinterpretation of the proprietary name as "Qlosl" or "Qiosi." Graphic designs should not distort critical information.[b]

[a] Getahun, S. Label and Labeling Review for Qlosi (NDA 217836). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 13. TTT ID No.: 2023-3264.

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

The Applicant intends to retain the proposed Graphic design based on the following rationale:

- *"The proprietary name candidate, Qlosi, underwent rigorous analysis and was compared to potentially similar names that were revealed in a POCA 4.3 search as well as a survey of likely healthcare practitioners that would come in contact with the product. None of the names were found to have significant look-alike or sound-alike similarity with Qlosi. (see NDA 217836, Request For Proprietary Name Review for QLOSI, Module 1.18)."*
- *"We believe there is minimal risk if there was confusion or misunderstanding 'l' for an 'i'. Qiosi is an odd sequence of letters that does not resemble any ophthalmic brand that could be mistaken or misunderstood by a health care professional within an EMR."*
- *"With significant professional promotion, similar to Xiidra, we believe QLOSI will be well understood in terms of spelling and pronunciation amongst eye care professionals. We plan to include the pronunciation in many of the promotional materials to ensure QLOSI is understood to be CLOH-SEE."*
- *"The distribution channel for QLOSI will be through a single specialty pharmacy so this will significantly reduce the risk of confusion when prescribing and fulfilling this prescription for a patient."*
- (b) (4)

However, we maintain our original recommendation to revise the presentation of the letter 'l' to minimize risk of misinterpretation.

Additionally, as part of our overall evaluation of the container label, and revised pouch, and carton labeling, we note DO recommend that the Applicant revise the package type term to "Single-Patient-Use Vial" instead of OPQ's recommended package type term of "Single-Dose Vial." We considered the use of the package type term "Single-Patient-Use" for this specific product, and we find that it is unacceptable from a medication error perspective. We note that Single-patient-use containers are containers intended to be used multiple times to administer multiple doses for a single patient.[c] Unit dose containers, (b) (4), are not resealable.[d] Thus, we are concerned that stating the package type term as "single-patient-use" gives the impression that patients can save an opened vial for later use (i.e., to administer the second dose 2-3 hours later). We confirmed with our OPQ colleagues that the opened vial should be discarded immediately after a single use. If a patient needs to repeat a dose, they should use a new vial to do so. As such, we agree with OPQ's original comment to revise to "single-dose vial," which appears more accurate for this container and intended handling.

[c] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/media/117883/download.

[d] Draft Guidance for Industry: Quality Consideration for Topical Ophthalmic Drug Products. October 2023. Available from: https://www.fda.gov/media/172937/download

3 CONCLUSION

The revised container labels, pouch and carton labeling are unacceptable from a medication error perspective as described above.

3.1 RECOMMENDATIONS FOR ORASIS PHARMACEUTICALS, LTD.

We recommend the following be implemented prior to approval of this NDA:

A. We reviewed your rationale to retain the graphic design incorporated in the proprietary name 'Qlosi', specifically in the lowercase letter 'l'. We considered the use of the graphic and risk of misinterpretation throughout the medication use process. As previously stated, the letter 'l' normally does not contain any dots to signify that it is the letter 'l' and graphic designs should not distort critical information (such as the proprietary name).[e] Therefore, we continue to recommend that you revise the graphic of the lowercase letter 'l' in the proprietary name to remove the dot graphic (i.e., the lowercase letter 'l' should be presented as one continuous stroke) to minimize misinterpretation with other graphics proposed for the proprietary name.

B. The (b) (4) vials are not resealable and as such, each vial should be discarded immediately after the first use.
    1. Revise the package type term from "Single-patient-use vial" to "Single-dose vial".
    2. Update the storage instructions to state "Discard each single-dose vial immediately after use."
    3. Revise the handling information in Sections 2 and 16 of the Prescribing Information to state to discard each single-dose vial immediately after use.

[e] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 5, 2023

To: Jacquelyn Smith, Regulatory Project Manager
Office of Regulatory Operations
Division of Regulatory Operations for Specialty Medicine (DROSM)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for QLOSI (pilocarpine hydrochloride ophthalmic solution) 0.4%, for topical ophthalmic use

NDA: 217836

Background:

In response to DROSM's consult request dated February 13, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for QLOSI (pilocarpine hydrochloride ophthalmic solution) 0.4%, for topical ophthalmic use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 28, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on September 28, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov.

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Clinical Inspection Summary

Date	August 15, 2023
From	Roy Blay, Ph.D. Michele Fedowitz, M.D. Jenn Sellers, M.D., Ph.D. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	William Boyd, M.D., Deputy Division Director Rhea Lloyd, M.D., Clinical Team Leader Jenna Hammer, M.D., Reviewing M.O. Lois Almoza, P.M. Division of Ophthalmology
NDA	217836
Applicant	Orasis Pharmaceuticals, Ltd.
Drug	Qlosi (pilocarpine hydrochloride ophthalmic solution 0.4%)
NME	No
Therapeutic Classification	Muscarinic cholinergic agonist
Proposed Indication(s)	Treatment of presbyopia in adults
Consultation Request Date	13 Feb 2023
Summary Goal Date	31 Aug 2023
Action Goal Date	22 Oct 2023
PDUFA Date	22 Oct 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Protocols 20-150-0002 (NEAR-1) and 20-150-0003 (NEAR-2) were submitted to the Agency in support of NDA 217836 for the use of Qlosi (pilocarpine hydrochloride ophthalmic solution 0.4%) for the treatment of presbyopia in adults. The clinical investigators, Drs. Debry and Restivo, were inspected in support of this NDA.

Based on the results of these inspections, the data generated by these two clinical sites appear adequate. However, protocol deviations regarding study drug administration and data discrepancies were observed at Dr. Restivo's site and were brought to the attention of the review division by email on 8/8/2023. We recommend that the review division conduct sensitivity analyses to determine the impact, if any, on study outcome.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Qlosi, a muscarinic cholinergic agonist, for the treatment of presbyopia in adults

Inspections were requested of the following protocols in support of this application:

Protocol Numbers and Titles:

Protocol 20-150-0002 titled "A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia" (the NEAR-1 study: Near Eye-vision Acuity Restoration),

and

Protocol 20-150-0003 titled "A Multi-Center, Double-Masked, Vehicle-Controlled, Evaluation of the Efficacy and Safety of CSF-1 in the Temporary Correction of Presbyopia" (the NEAR-2 study: Near Eye-vision Acuity)

20-150-0002 (NEAR-1) and 20-150-0003 (NEAR-2)

These essentially identical protocols were multicenter, randomized. double-masked, vehicle-controlled, parallel-group studies to evaluate the safety and efficacy of Qlosi (CSF-1, pilocarpine hydrochloride ophthalmic solution 0.4%) compared to vehicle in treating adults with presbyopia.

At Visit 1, subjects were screened for the study and were dosed with vehicle to rule out those subjects responding to vehicle. At Visit 2, qualifying subjects who were non-responsive to vehicle were randomized in a 1:1 ratio to Qlosi or vehicle followed by efficacy and safety assessments at specified timepoints following each of two doses. Similar assessments occurred at Visits 3 and 4.

The primary objective of the study was to evaluate the efficacy of Qlosi for the temporary correction of presbyopia while the primary efficacy endpoint was the percentage of subjects with a $\geq$ 3-line (15-letter) gained from baseline in Best Distance-Corrected Visual Acuity (BDCVA) at 40 cm and no loss in BDCVA $\geq$ 5 letters (Early Treatment Diabetic Retinopathy Study, ETDRS chart at 4 m) in the study eye at Visit 3, following Dose 1, 1 hour post-treatment.

Study 20-150-0002 was conducted from 18 Oct 2020 (first subject, first visit) to 19 Feb 2022 with the last visit of the last subject. The study was conducted at 18 domestic sites with 293 subjects completing the study.

Study 20-150-0003 was conducted from 16 Oct 2020 (first subject, first visit) to 09 Feb 2022 (last subject, last visit). The study was conducted at 18 domestic sites with 286 subjects completing the study.

III. RESULTS:

1. DeBry, Peter W.
NV Eye Surgery
2390 W. Horizon Ridge Pkwy.
Henderson NV 89052

Site: 21: Protocol 20-150-0002 (NEAR-1)
Inspection Dates: 15-22 May 2023

Dr. DeBry was inspected for the conduct of Protocol **20-150-0002 (NEAR-1).** This was the first inspection of Dr. DeBry. At this site, 103 subjects were screened, 46 subjects were enrolled, and 42 subjects were treated and completed the study.

The study files of 25 subjects were reviewed**,** including the verification of the visual acuity scores contributing to the determination of the primary efficacy endpoint as well as the reporting of adverse events. Subject records reviewed included study eligibility, informed consent, protocol adherence, protocol deviations, and concomitant medications.

Study related documents reviewed included Form 1572s, IRB, sponsor, and monitor correspondence, training documentation, delegation logs, investigational product (IP) receipt, storage, accountability, and dispensation records, electronic records including access controls and audit trails, and financial disclosures.

The inspection compared the source documents and electronic case report forms (eCRFs) with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

2. Restivo, Vincent A.
Hill Country Eye Center
11901 West Parmer Lane #400
Cedar Park, TX 78613

Site: 41: Protocol 20-150-0003 (NEAR-2)
Inspection Dates: 22-26 May 2023

Dr. Restivo was inspected for the conduct of Protocol **20-150-0003 (NEAR-2)**. This was the first inspection of Dr. Restivo. At this site, 46 subjects were consented, 16 subjects were screen failures, one subject was lost to follow up, and 29 subjects were randomized to the study. Two subjects later withdrew consent, and one subject discontinued due to an adverse event, resulting in 26 subjects completing the study.

The study files of the 29 randomized subjects were reviewed, including the visual acuity scores contributing to the determination of the primary efficacy endpoint as well as the reporting of adverse events. Subject records reviewed included study eligibility, medical histories, informed consent, protocol deviations, and concomitant medications.

Study related documents reviewed included Form 1572s, IRB correspondence and approvals, training documentation, delegation logs, IP shipment, storage, accountability, and dispensation records, sponsor and monitor correspondence, electronic records including access controls and audit trails, and financial disclosures.

The inspection compared the source records and eCRFs with the data listings. Review of these documents revealed unreported non-serious adverse events and protocol deviations, and the discrepancies in visual acuity data, as described below.

There were two non-serious adverse events in two subjects that were documented in the source records, but not reported to the Sponsor, as shown in Table 1:

Table 1. Unreported Non-serious Adverse Events

Subject	Date	Adverse Event	Source	eCRF
(b) (6)		Foreign body sensation after drop instillation OU (both eyes)	YES	NO
		Burning with drop instillation OU (both eyes) after dose 1 and 2 for 3-5 minutes	YES	NO

Reviewer's Note: As noted in the product labeling, instillation pain is a common adverse reaction, and it appears unlikely that these isolated events would impact the safety profile of Qlosi (pilocarpine hydrochloride ophthalmic solution 0.4%), which is not an NME, and the safety profile has been established.

There were six subjects who did not complete IP administration according to the protocol and these protocol deviations were not reported. Specifically, between Visits 2 & 3, subjects were to take their first dose in the morning and the second dose was to occur 2 hours (+1 hour) after the first dose and between Visits 3 & 4, subjects were to take their first dose in the morning and their second dose was to occur 3 hours (+1 hour) after the first dose. The following table (Table 2) shows the deviations as recorded in the subjects' dosing diaries:

Table 2. Protocol Deviations with Respect to the Timing of IP Administration

Subject	Visit Range	Date	1st Dose	2nd Dose	Out of Time Range
(b) (6)	2 & 3			(b) (6)	2 minutes
	3 & 4				No AM dose
	2 & 3				24 minutes
	2 & 3				5 minutes
	3 & 4				Dose missed
	2 & 3				17 minutes & No AM dose

(b) (6)	3 & 4	(b) (6)	40 minutes & No AM dose
	2 & 3		2 hours & 20 minutes & No AM dose
	3 & 4		1 hours & 30 minutes
	3 & 4		Dose missed
	2 & 3		No AM dose

Reviewer's Note: These unreported protocol deviations were brought to the attention of the review division by email on 8/8/2023 for their assessment of the impact, if any, on study outcome.

There were discrepancies between the source documentation of visual acuity data and the data reported to the Agency for five subjects as shown in Tables 3 and 4:

Table 3. Transcription Errors of Visual Acuity Data

Subject	Visit, Timepoint, Eye	Measurement ID	Source	EDC	Line Listings	Suspected Error
(b) (6)	Visit 4, 5-Hour, OS	BDCVA 40 cm	+0.12	+0.26	+0.26	Transcription
	Visit 3, 1-Hour, OS	ETDRS 4 m	-0.06	-0.29	-0.29	Transcription
	Visit 2, 2-Hour, OD	BDCVA 40 cm	+0.08	-0.08	-0.08	Transcription

Table 4. Miscalculations of Visual Acuity Data

Subject	Visit, Timepoint, Eye	Measurement ID	Source	Corrected Measurement	Suspected Error
(b) (6)	Visit 2, Pre-treat, OS	ETDRS 4 m	0	Should be +0.02	Calculation
	Visit 3, Pre-treat, OD	BDCVA 40 cm	+0.38	Should be +0.34	Calculation

Reviewer's Note: Review of the inspection report exhibits related to the above two subjects documented calculation errors: a miscount of letters misidentified on vision testing and the use of the wrong multiplicand in LogMAR determination for Subjects (b) (6) *respectively. These discrepancies were brought to the attention of the review division by email on 8/8/2023 for their assessment of the impact, if any, on study outcome.*

Dr. Restivo submitted a written response to the inspection observations acknowledging the deficiencies and noted the implementation of additional training and quality control checks, a limitation on the number of clinical studies being conducted concurrently, the issuance of new SOPs addressing the scheduling of study activities and completion of source documents, and the hiring of new personnel to help address workload issues.

Reviewer's Note: Dr. Restivo's response and proposed corrective actions appear adequate.

Other that the discrepancies outlined above, adherence to the regulations and the investigational plan appeared adequate.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
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OSI/Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Michele Fedowitz
OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 13, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217836
Product Name and Strength:	Qlosi[a] (pilocarpine hydrochloride) ophthalmic solution, 0.4%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Orasis Pharmaceuticals, Ltd.
FDA Received Date:	December 22, 2022,
TTT ID #:	2023-3264
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

[a] The proprietary name for this NDA, Qlosi was found conditionally acceptable on April 27, 2023.

1 REASON FOR REVIEW

As part of the approval process for Qlosi (pilocarpine hydrochloride) ophthalmic solution, the Division of Ophthalmology (DO) requested that we review the proposed Qlosi prescribing information, container label, pouch and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (For Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed container label, pouch and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Orasis Pharmaceuticals, Ltd..

4 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, under *Section 17 Patient Counseling Information* we note the statement *"Contact lens should be removed prior to the instillation of Qlosi. Wait 10 minutes after dosing before reinserting contact lenses."*	This information is also relevant to include in Section 2. See *Draft Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.*[b]	We recommend including the statement in Section 2 of the PI. Additionally, we recommend revising to active voice. For example, *"Remove contact lens prior to the instillation of Qlosi. Wait 10 minutes after dosing before reinserting contact lenses."* Include following the sentence *"Qlosi can be administered on a daily basis, or as needed, up to twice each day."* Note, revising the statement to active voice is also applicable to Section 17.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented, the appropriate information to facilitate identification of the proposed dosage form is not included.	A description of identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(4)(ii).	Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57(c)(4)(ii).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented the appropriate information to facilitate identification of the	A description of the identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57 (c)(17)(iii).	Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in

[b] Draft Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. 2023. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dosage-and-administration-section-labeling-human-prescription-drug-and-biological-products-content

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	dosage form is not included.		accordance with 21 CFR 201.57 (c)(17)(iii).
2.	Storage statements are written in passive voice (e.g., "Once a pouch is open, single-use vials *should* be used within 30 days" and "Opened vials *should* be discarded immediately after use.")	Passive voice may lead to ambiguity in how to properly store and handle the product, which could lead to storage errors.	We recommend revising to active voice, for example: "Once a pouch is open, use single-use vials within 30 days." AND "Discard opened vials immediately after use."

5 RECOMMENDATIONS FOR ORASIS PHARMACEUTICALS, LTD.

Table 3. Identified Issues and Recommendations for Orasis Pharmaceuticals, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label, Pouch, and Carton Labeling			
1.	As currently presented, the dot used to represent the lower-case dotted letter 'i,' is also used to represent the lower case 'l' which may lead to misinterpretation of the proprietary name. (b) (4)	Graphic designs should not distort critical information.[c] As proposed, the letters "l" and "i" could lead to misinterpretation of the name as "Qlosl" or "Qiosi".	To prevent misinterpretation of the proprietary name, we recommend removing the dot that is used beneath the lower-case letter 'l.'

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 3. Identified Issues and Recommendations for Orasis Pharmaceuticals, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented the format for expiration date is not defined on the pouch and carton labeling. Additionally, intended location for the expiration date is not identified on the container label.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors. Furthermore, product expiration date is also required on the immediate container label per 21 CFR 201.17.	Identify the expiration date format you intend to use on the pouch and carton labeling. Additionally, identify intended location and format of expiration date you intend to use on the container label per 21 CFR 201.17. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
3.	As currently presented, the linear barcode is missing.	Required per 21 CFR 201.25. The drug barcode is often used as an additional	Add the product's the linear barcode per 21 CFR 201.25. Please note, the barcode should be surrounded by

Table 3. Identified Issues and Recommendations for Orasis Pharmaceuticals, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		verification before drug administration in the hospital setting; therefore, it is important safety feature that should be part of the label.	sufficient white space to allow scanners to correctly read the barcode as well as in an area where it will not be damaged.
Container Label			
1.	As currently presented, the intended location of the lot number is not identified.	The lot number statement is required on the immediate container label per 21 CFR 201.10(i)(1).	Identify the intended location of the lot number statement. When determining this placement please ensure that there are no other numbers located in close proximity to the lot number or expiration date that can be mistaken as the lot number or expiration date.
Carton Labeling			
1.	As currently presented, we note that the product identifier is not included on the carton labeling.	The Drug supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifier recommends a machine-readable (2D data matrix barcode) product identifier	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers* (July 2021).[d] If you determine that the product identifier requirements apply to your product's labeling, add a

[d] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers

Table 3. Identified Issues and Recommendations for Orasis Pharmaceuticals, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		and a human-readable product identifier. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] Serial: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]	placeholder for the product identifier on the pouch and carton labeling. Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.
Pouch Labeling			
1.	As currently presented, a space is not provided for users to write in the date of first opening of the pouch.	Lack of an allotted space to write in the date of first opening of the pouch may lead to storage and administration errors (e.g., use of vials beyond 30 days).	We recommend including the statement "Date of first opening __/__/__. Additionally, we recommend revising the discard statement to active voice, for example, "*Once pouch is open, discard unused vials after 30 days.* Date of first opening __/__/__. *Discard the opened single-use vial immediately after use"*
Carton Labeling			
1.	As currently presented, the statement of dosage includes the term "(b) (4)."	The term "(b) (4) is inconsistent with the terminology used in the Prescribing Information.	Revise the term "(b) (4) (b) (4)" in the statement of dosage to "Prescribing Information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Qlosi that Orasis Pharmaceuticals, Ltd. submitted on December 22, 2022.

Table 4. Relevant Product Information for Qlosi	
Initial Approval Date	N/A
Active Ingredient	Pilocarpine hydrochloride
Indication	Treatment of presbyopia in adults
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic solution
Strength	0.4%
Dose and Frequency	Instill one drop of Qlosi in each eye. This can be repeated a second time after 2-3 hours for an effect up to 8 hours. Qlosi can be administered on a daily basis, or as needed, up to twice each day.
How Supplied	Qlosi is supplied as a sterile, preservative-free ophthalmic solution in configurations of 5 single-use vials of 0.4 mL fill. Each single-use vial is comprised of transparent low-density polyethylene (LDPE). 5 single-use vials are packaged in a foil pouch. Qlosi is supplied in a carton containing X[e] pouches. (NDC ####-####-##)
Storage	Store refrigerated at 36°F to 46°F (2°C to 8°C). Product may also be stored at room temperature [up to 77°F (25°C)] for up to 30 days. Once a pouch is open, single-use vials should be used within 30 days. Store unused product away from light. Opened vials should be discarded (b) (4) after use.
Container Closure	Low-density polyethylene (LDPE) vial.

[e] Per the Applicant, the number of pouches will be updated to align with the final chosen presentation for Qlosi.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 20, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, pilocarpine, pilocarpine hydrochloride, and NDA 217836. Our search did not identify any previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Qlosi labels and labeling submitted by Orasis Pharmaceuticals, Ltd..

- Container label received on December 22, 2022
- Pouch labeling received on December 22, 2022
- Carton labeling received on December 22, 2022
- Prescribing Information (Image not shown) received on December 22, 2022, available from: \\CDSESUB1\EVSPROD\nda217836\0001\m1\us\114-labeling\draft\labeling\clean-draft-labeling.docx

F.2 Label and Labeling Images

Container label

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name: (b) (4)
City, State: (b) (4)
Assignment Date: (b) (4)
EI Start Date: (b) (4)
EI End Date: (b) (4)
FDA Participants: Jeanne J. Thai, Erin M. McDowell

Inspection Type: Surveillance
FDA – 483 Issued: Yes

Final Recommendation: Data is Reliable

Inspection Summary

This was a FY2023 GLP Surveillance inspection of (b) (4) The current inspection covered studies Non-responsive and 21-1296 (NDA-217836). A three item Form FDA 483 was issued at the inspection close-out. Two items were also discussed with the firm's management. The audited studies are reliable for Agency review.

Studies Audited during this Inspection

Non-responsive

Study No.: 21-1296
Study Title: 28-Day Topical Ocular Toxicity Study of CSF-1 (Pilocarpine HCl 0.4% w/v Ophthalmic Solution) Containing Elevated Levels of (b) (4) and (b) (4) Impurities in Dutch-Belted Rabbits
Study Initiation Date: 9/27/2021
Final Report Date: 11/30/2022
Study Director: (b) (4)
IND/NDA/BLA/ANDA No.: NDA 217836
Review Division: CDER/OND/OSM/DO
Sponsor: Orasis Pharmaceuticals, Ltd., Herzliya, Israel

Background:

(b) (4) operates as a nonclinical laboratory conducting phases of In Vivo Toxicology studies that are submitted to FDA in support of CDER applications. Approximately 90% of the firm's workload is GLP compliant.

Prior Inspection:
The previous inspection of the firm occurred (b) (4) That inspection was classified as Voluntary Action Indicated (VAI). (b) (4)

(b) (4)

Current Inspection:
Studies audited during the current inspection are listed above.

In addition to data auditing, the following areas were covered: Test Facilities & Operations, Equipment, Archival and Quality Assurance Practices, SOPs, Study Practices, Animal Care, and the Personnel Training Program.

At the inspection closeout meeting, a three item Form FDA 483 was issued to the firm's management. Additionally, two items were discussed with the firm's management. The observations, discussion items, a summary of the firm's written response dated (b) (4) and our evaluation follow.

OBSERVATION #1:
(b) (4)

Firm's Response:
(b) (4)

OSIS Evaluation:
(b) (4) This observation did not impact data quality or integrity (b) (4)

(b) (4)

(b) (4)

OSIS Evaluation:

(b) (4). The firm's response adequately addressed (b) (4) This discussion item has no impact on data reliability of the audited studies.

Recommendations:

- Data from the audited studies are reliable and the reviewer recommends that the studies be accepted for Agency review.
- The firm's response is adequate.
- The next surveillance inspection should be scheduled in FY2025.

Draft: EM 04/28/2023, 05/09/2023
Edits: ZC 04/28/2023, 05/09/2023; CB 05/11/2023
ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/GLP Program/(b) (4)
(b) (4)/Post-Inspection Folder/EIR & EIR Review
OSIS File #: GLP (b) (4)
eNSpect OP ID: (b) (4)
FEI: (b) (4)

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